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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/801,944 | 03/08/2001 | Gabriel Vogeli | PHRM0008-100/00100.US1 | 5364 |

34135 7590 12/06/2004

COZEN O ' CONNOR, P.C.
1900 MARKET STREET
PHILADELPHIA, PA 19103-3508

| EXAMINER | |
|---|---|
| LI, RUIXIANG | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1646 | |

DATE MAILED: 12/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/801,944 | VOGELI ET AL. | |
| | Examiner | Art Unit | |
| | Ruixiang Li | 1646 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *12 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-87 and 91-95* is/are pending in the application.

4a) Of the above claim(s) *1-29,36-87 and 91-95* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 06/11/2001 and 10/19/2001
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence alignment*.

## DETAILED ACTION

### *Election/Restrictions*

1. Applicants' election with traverse of Group II, Claims 30-35 and 88-90, and the polypeptide of SEQ ID NO: 268 on 10/12/2004 is acknowledged. The traversal is on the grounds that searching both the nucleic acid and the isolated polypeptide would not represent an undue burden and would serve to reduce administrative inefficiencies, both on the part of the Office and of Applicants. This is not found to be persuasive because polypeptide of SEQ ID NO: 268 and the nucleic acid encoding the polypeptide are distinct chemical entities; they have completely different structures and biological functions. Search and consideration of both the polypeptide and the nucleic acid encoding the polypeptide constitutes an undue burden on the office.

   The requirement is still deemed proper and is therefore made FINAL.

2. Applicants' preliminary amendment to the specification filed on 08/04/2003 has been entered. Applicants' preliminary amendment filed on 10/12/2004 has also been entered. Claims 88-90 have been canceled. Claims 31-34 have been amended. Claims 1-87 and 91-95 are pending. Claims 30-35 are are under consideration. All other claims are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

***Information Disclosure Statement***

3. The information disclosure statements filed on 06/11/2001 and 10/19/2001 have been considered by the Examiner and a signed copy of form PTO-1449 is attached to the office action.

***Rejections—35 USC § 101***

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claims 30-35 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

Claims 30-35 are drawn to an isolated polypeptide comprising an amino acid sequence at least 90% or 95% homologous to SEQ ID NO: 268. The claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. A specific and substantial utility is one that is particular to the subject matter claimed and that identifies a "real world" context of use for the claimed invention which does not require further research.

The instant specification discloses the polypeptide of SEQ ID NO: 268 and the nucleic acid encoding the polypeptide. Nonetheless, the instant disclosure fails to provide any sufficient information or evidence on the specific biological functions or physiological significance of the molecules of the present invention and fails to disclose a patentable utility for the claimed invention.

First, the invention lacks a well-established utility. A well-established utility is a specific, substantial, and creditable utility that is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material. The sequence and prior art search does not reveal that the polypeptide of SEQ ID NO: 268 or the nucleic acid encoding the polypeptide has any well-established biological functions or any physiological significance. While the polypeptide of SEQ ID NO: 268 can be reasonably placed within the GPCR family based upon sequence homology, it is impossible to predict precisely protein functions solely based upon sequence homology in view of the diversity of structure and functions of the GPCR proteins (Peer Bork and Eugene V. Koonin, Predicting functions from protein sequences—where are the bottlenecks? *Nature Genetics* 18:313-318,1998; Ji et al., G protein-coupled receptors. J. Biol. Chem. 273:17299-17302, 1998). Au-Young et al. (US20030211493 A1, Publication date: November 2003; 102 (e) date: February 11, 2000) teach a polypeptide, which is 100% identical to the instantly claimed polypeptide of SEQ ID NO: 2. However, Au-Young et al. do not appear to teach the specific biological functions of the polypeptide of SEQ ID NO: 268 and does not provide a specific and substantial utility for the instantly claimed polypeptide. No art of record discloses or suggests any property or activity for the claimed molecules such that another non-asserted utility would be well-established for the claimed invention.

Secondly, the specification does not disclose a specific and substantial utility for the present invention. The specification asserts, for example, that the present

invention provides a method of identifying a compound that binds to the polypeptide of SEQ ID NO: 268 or the nucleic acid encoding the polupeptide, or a compound that modulates the activity of the polypeptide (pages 4-7 of the specification). The specification also asserts that the present invention may be used for diagnosis or treatment of a long list of disorders (pages 5, 40, 50, 59, and 62). These asserted utilities are not specific and substantial because they do not identify or reasonably confirm a "real world" context of use. The disclosure neither identifies the biological functions (e.g., as a pain receptor as asserted in claim 33) of the claimed molecules nor a causative link between the polypeptide of SEQ ID NO: 268 and a specific disorder. Clearly, further research would be required to determine the functions of the claimed molecules or to identify a disease that can be treated or diagnosed with the claimed molecules See *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966), noting "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."

Accordingly, the claimed invention is not supported by a specific and substantial asserted utility or a well-established utility.

6. Claims 30-35 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Furthermore, even if the polypeptide of SEQ ID NO: 268 were to have a patentable utility, the instant disclosure would not be found to be enabling for the full scope of the invention of claims 30 and 32-35.

The factors that are considered when determining whether a disclosure satisfies enablement requirement include: (i) the quantity of experimentation necessary; (ii) the amount of direction or guidance presented; (iii) the existence of working examples; (iv) the nature of the invention; (v) the state of the prior art; (vi) the relative skill of those in the art; (vii) the predictability or unpredictability of the art; and (viii) the breadth of the claims. *Ex Parte Forman*, 230 USPQ 546 (Bd Pat. App. & Int. 1986); *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Claims 30 and 32-35 are drawn to an isolated polypeptide comprising an amino acid sequence at least 90% or 95% homologous to SEQ ID NO: 268. There is no specific functional limitation or any particular conserved structure recited in the claims. However, other than the polypeptide sequence of SEQ ID NO: 268 and the nucleic acid encoding the polypeptide, the instant disclosure fails to provide sufficient guidance, information or working examples regarding the structural and functional requirements commensurate in scope with what is encompassed by the instant claims. The disclosure does not show (i) which portions of SEQ ID NO: 268 are critical to the activity of the polypeptide of SEQ ID NO: 268; and (ii) what modifications (e.g., substitutions, deletions or additions) one can make to SEQ ID NO: 268 will result in protein mutants with the same functions as that of the polypeptide of SEQ ID NO: 268. The state of the art (See, e.g., Ngo, et al, *The*

*Protein Folding Problem and Tertiary Structure Prediction*, 1994, Merz, et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495) is such that the relationship between sequence of a protein and its activity is not well understood and is not predictable. Excising out portions of a protein or modifications to a protein, e.g., by substitutions or deletions, would often result in deleterious effects to the overall activity and effectiveness of the protein.

It is noted that claim 33 recites "wherein said polypeptide encodes a pain receptor", whereas claim 34 recites "wherein said polypeptide is a mammalian GPCR involved in disease or disorders related pain". However, the specification fails to provide any sufficient information on the function (e.g., as a pain receptor) of the polypeptide set forth in SEQ ID NO: 286; there is no disclosure of a causative link between overexpression (or a low level of expression) of polypeptide and a specific disease related to pain. Thus, the limitations do not effectively limit the scope of the claims.

Since the disclosure fails to provide sufficient guidance/directions to enable one skilled in the art to predict which if any homologues of the polypeptide of SEQ ID NO: 268 would be reasonably expected to retain characteristic activities of SEQ ID NO: 268 and the general disclosure that one could make and use SEQ ID NO: 268 (as noted above, assuming there is a patentable utility for the polypeptide of SEQ ID NO: 268) could not be used to be such guidance as to guide one skilled in the art to make and use the invention commensurate in scope with the claims, it would require

undue experimentation for one skilled in the art to make and use the claimed genus of polypeptide embraced by the instant claims.

### *Claim Rejections—35 USC § 112, 1st paragraph*

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 30 and 32-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

Claims 30 and 32-35 are drawn to an isolated polypeptide having at least 90% or 95% sequence identity to the polypeptide of SEQ ID NO: 268. The claims do not require that the polypeptide possess any particular biological activity, nor any particular conserved structure, nor other disclosed distinguishing feature. Thus, the

claims are drawn to a genus of polypeptides that is defined only by a partial structure in the form of a recitation of percent identity.

The instant disclosure of an isolated polypeptide of SEQ ID NO: 268 and its encoding nucleic acid molecule does not adequately support the scope of the claimed genus, which encompasses a substantial variety of homologues or variants of the polypeptide of SEQ ID NO: 268. A description of a genus of cDNA may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The instant disclosure fails to provide sufficient description information, such as definitive structural or functional features of the claimed genus of polypeptides. There is no description of the conserved regions that are critical to the structure and function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Since there is no disclosure on the specific biological functions of the claimed polypeptide, the limitation "a pain receptor" or "a mammalian GPCR involded in disease or disorders relating to pain" does not effectively limit the scope of the claimed invention. Furthermore, the prior art does not provide compensatory structural or correlative teachings to enable one skilled in the art to identify the encompassed polypeptides as being identical to those instantly claimed.

Due to the breadth of the claimed genus and lack of the definitive structural or functional features of the claimed genus, one skilled in the art would not recognize from the disclosure that the applicant was in possession of the claimed genus. Accordingly, only the isolated polypeptide comprising SEQ ID NO: 268, but not the full breadth of the claims meets the written description provision of 35 U.S.C. §112, first paragraph.

9. Claim 33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The amended claim 33 recite a new limitation "a pain receptor". However, there is no sufficient support for such a limitation.

***Claim Rejections—35 USC § 112, 2nd paragraph***

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 33-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 33 is indefinite because it recites "wherein said polypeptide encodes a pain receptor". It is known in the art that a nucleic acid encodes a polypeptide. A polypeptide does not encode a polypeptide receptor. In addition, it is unclear what

the metes and bounds of the term "a pain receptor" are because there is no support and definition for the term in the specification. Thus, the recitation is confusing, rendering the claim indefinite.

Claim 34 is indefinite because it recites the limitation "wherein said polypeptide is a mammalian GPCR involved in disease or disorders relating to pain". It is unclear what the metes and bounds of the limitation are because the word "involved" is ambiguous. It is unclear whether the limitation means there is a causative link between overexpression (or a low level of expression) of polypeptide and a disease related to pain.

Claim 35 is rejected as a dependent claim from claim 34.

***Claim Rejections—35 USC § 102***

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

13. Claims 30-35 are rejected under 35 U.S.C. 102(e) as being anticipated by Au-Young et al. (US20030211493 A1, Publication date: November 2003; 102 (e) date: February 11, 2000).

Au-Young et al. teach a polypeptide, which is 100% identical to the instantly claimed polypeptide of SEQ ID NO: 2 (see attached sequence alignment). Au-Young

et al. also teach a composition comprising the polypeptide and a pharmaceutically acceptable excipient ([0026]). Since the polypeptide taught by Au-Young et al. is identical to the polypeptide of SEQ ID NO: 2, the polypeptide of Au-Young et al. is capable of being used for the intended use or having the property as recited in claims 33 and 34. Therefore, the reference of Au-Young et al. meets the limitations of claims 30-35.

***Conclusion***

14. No claims are allowed.

***Advisory Information***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (571) 272-0875. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you

have questions on access to the Private PAIR system, please contact the Electronic Business Center (EBC) at the toll-free phone number 866-217-9197.

Ruixiang Li

Ruixiang Li, Ph.D.
Examiner
December 1, 2004

```
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RESULT 12
US-10-237-467-8
; Sequence 8, Application US/10237467
; Publication No. US20030186324A1
; GENERAL INFORMATION:
;  APPLICANT: Liao, Jiayu
;  APPLICANT:  Gray, Nathanael S.
;  APPLICANT:  Caldwell, Jeremy C.
;  APPLICANT:  Schultz, Peter G.
;  APPLICANT:  IRM LLC
;  TITLE OF INVENTION: Sensory Neuron Receptors
;  FILE REFERENCE: 021288-001300US
;  CURRENT APPLICATION NUMBER: US/10/237,467
;  CURRENT FILING DATE:  2003-01-14
;  PRIOR APPLICATION NUMBER: US 60/317,879
;  PRIOR FILING DATE: 2001-09-07
;  NUMBER OF SEQ ID NOS: 18
;  SOFTWARE: PatentIn Ver. 2.1
; SEQ ID NO 8
;   LENGTH: 321
;   TYPE: PRT
;   ORGANISM: Homo sapiens
;   FEATURE:
;   OTHER INFORMATION: dorsal root ganglia G-protein coupled receptor (GPCR)
;   OTHER INFORMATION: 6 (DRG6) (X54KRCBYJQ4)
US-10-237-467-8

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  Matches  321;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

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RESULT 13
US-10-182-822A-18
; Sequence 18, Application US/10182822A
; Publication No. US20030211493A1
; GENERAL INFORMATION:
;  APPLICANT: INCYTE GENOMICS, INC.; BAUGHN, Mariah R.
;  APPLICANT:  AU-YOUNG, Janice; YUE, Henry
;  TITLE OF INVENTION: G-PROTEIN COUPLED RECEPTORS
;  FILE REFERENCE: PI-0032 USN
;  CURRENT APPLICATION NUMBER: US/10/182,822A
;  CURRENT FILING DATE:  2001-02-01
;  PRIOR APPLICATION NUMBER: PCT/US 01/03455
;  PRIOR FILING DATE: 2001-01-02
;  PRIOR APPLICATION NUMBER: US 60/180,093
;  PRIOR FILING DATE: 2000-02-02
;  PRIOR APPLICATION NUMBER: US 60/182,045
;  PRIOR FILING DATE: 2000-02-11
;  NUMBER OF SEQ ID NOS: 42
;  SOFTWARE: PERL Program
; SEQ ID NO 18
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;   TYPE: PRT
;   ORGANISM: Homo sapiens
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;   NAME/KEY: misc_feature
;   OTHER INFORMATION: Incyte ID No: 7472136CD1
US-10-182-822A-18

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RESULT 14
US-10-343-650A-42
; Sequence 42, Application US/10343650A
; Publication No. US20040067499A1
; GENERAL INFORMATION:
;  APPLICANT: HAGA, TATSUYA
;  TITLE OF INVENTION: NOVEL G-PROTEIN COUPLED RECEPTOR
;  FILE REFERENCE: 31671-186347
;  CURRENT APPLICATION NUMBER: US/10/343,650A
;  CURRENT FILING DATE:  2003-07-21
;  PRIOR APPLICATION NUMBER: JP 2000/237818
;  PRIOR FILING DATE: 2000-08-04
;  PRIOR APPLICATION NUMBER: JP 2001/34434
;  PRIOR FILING DATE: 2001-02-13
;  NUMBER OF SEQ ID NOS: 694
;  SOFTWARE: PatentIn Ver. 2.1
; SEQ ID NO 42
;   LENGTH: 321
;   TYPE: PRT
;   ORGANISM: Homo sapiens
US-10-343-650A-42

  Query Match           100.0%;  Score 1661;  DB 15;  Length 321;
  Best Local Similarity  100.0%;  Pred. No. 1.3e-145;
  Matches  321;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;
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← Yes. SEQ ID NO: 268 is present

PI-0036 P

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His Phe Val Ser Ile Leu Ser Phe Ser Glu Leu Gly Tyr Thr Ala
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Ala Thr Ile Pro Lys Met Leu Ala Asn Leu Leu Ser Glu Lys Lys
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Thr Ile Ser Phe Ser Gly Cys Leu Leu Gln Ile Tyr Phe Phe His
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Ser Leu Gly Ala Thr Glu Cys Tyr Leu Leu Thr Ala Met Ala Tyr
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Asp Arg Tyr Leu Ala Ile Cys Arg Pro Leu His Tyr Pro Thr Leu
125 130 135
Met Thr Pro Thr Leu Cys Ala Glu Ile Ala Ile Gly Cys Trp Leu
140 145 150
Gly Gly Leu Ala Gly Pro Val Val Glu Ile Ser Leu Ile Ser Arg
155 160 165
Leu Pro Phe Cys Gly Pro Asn Arg Ile Gln His Val Phe Cys Asp
170 175 180
Phe Pro Pro Val Leu Ser Leu Ala Cys Thr Asp Thr Ser Ile Asn
185 190 195
Val Leu Val Asp Phe Val Ile Asn Ser Cys Lys Ile Leu Ala Thr
200 205 210
Phe Leu Leu Ile Leu Cys Ser Tyr Val Gln Ile Ile Cys Thr Val
215 220 225
Leu Arg Ile Pro Ser Ala Ala Gly Lys Arg Lys Ala Ile Ser Thr
230 235 240
Cys Ala Ser His Phe Thr Val Val Leu Ile Phe Tyr Gly Ser Ile
245 250 255
Leu Ser Met Tyr Val Gln Leu Lys Lys Ser Tyr Ser Leu Asp Tyr
260 265 270
Asp Gln Ala Leu Ala Val Val Tyr Ser Val Leu Thr Pro Phe Leu
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60/182,045 filed on 2000-02-11

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35 40 45
Ser Met Val Ile Trp Leu Leu Gly Phe Arg Met His Arg Asn Pro
50 55 60
Phe Cys Ile Tyr Ile Leu Asn Leu Ala Ala Ala Asp Leu Leu Phe
65 70 75
Leu Phe Ser Met Ala Ser Thr Leu Ser Leu Glu Thr Gln Pro Leu
80 85 90
Val Asn Thr Thr Asp Lys Val His Glu Leu Met Lys Arg Leu Met
95 100 105
Tyr Phe Ala Tyr Thr Val Gly Leu Ser Leu Leu Thr Ala Ile Ser
110 115 120
Thr Gln Arg Cys Leu Ser Val Leu Phe Pro Ile Trp Phe Lys Cys
125 130 135
His Arg Pro Arg His Leu Ser Ala Trp Val Cys Gly Leu Leu Trp
140 145 150
Thr Leu Cys Leu Leu Met Asn Gly Leu Thr Ser Ser Phe Cys Ser
155 160 165
Lys Phe Leu Lys Phe Asn Glu Asp Arg Cys Phe Arg Val Asp Met
170 175 180
Val Gln Ala Ala Leu Ile Met Gly Val Leu Thr Pro Val Met Thr
185 190 195
Leu Ser Ser Leu Thr Leu Phe Val Trp Val Arg Arg Ser Ser Gln
200 205 210
Gln Trp Arg Arg Gln Pro Thr Arg Leu Phe Val Val Val Leu Ala
215 220 225
Ser Val Leu Val Phe Leu Ile Cys Ser Leu Pro Leu Ser Ile Tyr
230 235 240
Trp Phe Val Leu Tyr Trp Leu Ser Leu Pro Pro Glu Met Gln Val
245 250 255
Leu Cys Phe Ser Leu Ser Arg Leu Ser Ser Ser Val Ser Ser Ser
260 265 270
Ala Asn Pro Val Ile Tyr Phe Leu Val Gly Ser Arg Arg Ser His
275 280 285
Arg Leu Pro Thr Arg Ser Leu Gly Thr Val Leu Gln Gln Ala Leu
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